IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

Cellectis S.A.,

Plaintiff,

v.

Precision BioSciences, Inc.,

Defendant.

Civil Action No. 1:11-cv-00173-SLR-MPT

EXPERT DECLARATION OF DAVID EDGELL, PH.D. ON THE MEANING OF CLAIM TERMS IN CELLECTIS'S '372 PATENT

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Dated: August 15, 2012

I, David Edgell, Ph.D., hereby declare and state as follows:

1. I am submitting this declaration on behalf of Cellectis S.A. ("Cellectis") in the litigation identified on the foregoing page. I understand that Cellectis has accused Precision BioSciences, Inc. ("Precision") of infringing claims in Cellectis's United States Patent No. 7,897,372 ("the '372 patent"), entitled "I-CreI Meganuclease Variants with Modified Specificity, Method of Preparation and Uses Thereof." A copy of the '372 patent is attached to this declaration as **Exhibit 1**.

2. I have been asked to consider how one of ordinary skill in the art to which the '372 patent is directed would understand terms in the claims of the '372 patent. This declaration summarizes my opinions regarding those questions.

3. I understand that further expert discovery will occur at a later stage in this case, including the submission of expert reports on the infringement and validity of the '372 patent. I reserve my right to update my opinions in this declaration regarding the meaning of the claims of the '372 patent through any further expert reports and/or testimony that I may provide in this case, such as on infringement, validity or claim meaning.

QUALIFICATIONS

4. I am a tenured Associate Professor in the Department of Biochemistry at Schulich School of Medicine & Dentistry at The University of Western Ontario. My research focuses on the evolution of homing endonuclease structure and function and redesign of LAGLIDADG homing endonucleases for genome engineering. I have published dozens of peer-reviewed articles in these areas.

5. More information about my qualifications and background (including a list of my publications) is set forth in my *curriculum vitae*, attached to this declaration as **Exhibit 2**.

6. Based on my experience, training and qualifications, I consider myself to be an expert in the homing endonuclease field, including the design and use of engineered endonucleases (also referred to as engineered meganucleases).

7. The fee I am charging for my services as an expert witness in this case is $450 per hour, plus expenses.

MATERIALS CONSIDERED

8. I considered the following materials in preparing the opinions set forth in this declaration: (a) the '372 patent, its specification and claims; (b) the original prosecution history of the '372 patent in the United States Patent & Trademark Office ("the PTO"); (c) the prosecution history of the '372 patent in the ongoing reexamination of the '372 patent in the PTO; and (d) prior art cited during the foregoing prosecutions. I also relied on my own training and experience as a scientist in the field to which the '372 patent is directed, along with my understanding of how one of ordinary skill in the art would understand the disclosure of the '372 patent.

9. I have also reviewed the parties' Joint Claim Construction Chart ("the Joint Chart") in connection with the preparation of this declaration.

PERSON OF ORDINARY SKILL IN THE ART

10. It is my opinion that a person of ordinary skill in the art to which the '372 patent is directed would be a person with an advanced degree (such as a master's degree) in the field of biology, molecular biology, biochemistry, biophysical chemistry or a similar field. Such a person would be familiar with protein structure, manipulation of DNA sequences, molecular design techniques and genetic selection. My opinion as to the definition of a person of ordinary skill in the art is as of March 15, 2005, which is the filing date of the first application that led to

the '372 patent. All of the opinions expressed in this declaration regarding the meaning of claims and/or claim terms are made from the viewpoint of a person of ordinary skill in the art as defined in this paragraph.

BACKGROUND OF THE '372 PATENT

11. The field of the '372 patent includes homing endonucleases generally, and engineered I-CreI meganuclease variants more specifically. Wild-type I-CreI is found in an algae known as *Chlamydomonas reinhardtii*.

12. At least in part because homing endonucleases, such as I-CreI, recognize lengthy DNA cleavage sites (*e.g.*, 22-24 base pairs ("bp") for I-CreI), they have been found to be useful in genetic engineering applications. They can be engineered to recognize specific DNA cleavage sites in the genome of an organism other than that in which they are found in nature. For example, such engineered meganucleases, including engineered I-CreI meganuclease variants, can be used to cleave the DNA in the genome of a cell (making a double-stranded break in the DNA), followed by insertion of another DNA of interest at the cleaved site. Alternatively, the engineered meganuclease can be used to generate a mutation, such as a deletion or insertion, if a DNA template is not provided to repair the double-stranded break. These techniques can be used in a whole host of genetic engineering applications, including gene therapy and antiviral therapy, as well as agricultural biotechnology (*e.g.*, addition or removal of a trait and/or protein production) and for use in the generation of transgenic organisms.

13. Methods of creating engineered meganucleases, particularly I-CreI meganuclease variants, for use in such genetic engineering applications as listed above are the focus of the '372 patent, as well as the meganuclease variants themselves. For example, the '372 patent is directed to a method of preparing I-CreI meganuclease variants having a modified DNA cleavage

specificity, as well as the I-CreI meganuclease variants themselves that are obtainable by the described methods. (The '372 patent at, *e.g.*, column 1, lines 13-16.) The '372 patent also is directed to applications of the described meganuclease variants either for cleaving DNA targets or for genetic engineering purposes. (The '372 patent at, *e.g.*, column 1, lines 16-19.) The '372 patent also concerns nucleic acids encoding such meganuclease variants, expression cassettes comprising those nucleic acids, vectors comprising such expression cassettes, and to cells, organisms, plants or animals (except humans) transformed by said vectors. (The '372 patent at, *e.g.*, column 1, lines 20-24.)

14. Wild-type I-CreI is a homodimer, comprising two monomers that are non-covalently associated with one another. Each monomer is comprised of 163 amino acids, which amino acid sequence is described in the '372 patent as SwissProt accession number P05725 or pdb accession code 1g9y. These designations identify the 163 amino acids in each monomer of wild-type I-CreI, which amino acids had been identified and were known to a person of ordinary skill in the art as of March 15, 2005. As set forth in the '372 patent, wild-type I-CreI recognizes a semi-palindromic 22 bp target sequence and will cleave that sequence or site. (The '372 patent at, *e.g.*, column 2, lines 20-25.) *See* **Figure 1** (attached).

15. The '372 patent describes methods for preparing I-CreI meganuclease variants, which methods result in a meganuclease variant having amino acid mutations at least at certain specified positions in the 163 amino acid sequence of wild-type I-CreI. There are 20 amino acids identified by well-known abbreviations to a person of ordinary skill in the art (Ala or A, Cys or C, Asp or D, Glu or E, Phe or F, Gly or G, His or H, Ile or I, Lys or K, Leu or L, Met or M, Asn or N, Pro or P, Gln or Q, Arg or R, Ser or S, Thr or T, Val or V, Trp or W, and Tyr or Y). Ala or A, for instance, is the abbreviation for the amino acid alanine, which is found in the

amino acid sequence of wild-type I-CreI. The '372 patent specifies a monomer of an I-CreI meganuclease variant, where the monomer (or domain) has at least one mutation, including at least one substitution at one or more of amino acid positions 44, 68 and/or 70, and the monomer has at least one additional mutation at one or more of amino acid positions 26, 28, 30, 32, 33 and/or 38 (with the foregoing positions measured by counting the amino acids relative to the wild-type I-CreI sequence). A substitution at one of the foregoing positions can constitute substituting one amino acid for the amino acid found at that position in wild-type I-CreI. An I-CreI meganuclease variant containing such a monomer according to the claims of the '372 patent has the ability to recognize and cleave a DNA target site that is not able to be cleaved, for example, by the wild-type I-CreI, under the same conditions. This change in the meganuclease variant is referred to as "modified DNA cleavage specificity," which is defined in the '372 patent. For example, the '372 patent states that "[t]he term 'modified specificity' relates to a meganuclease variant able to cleave a homing site that is not cleaved, in the same conditions by the initial meganuclease (scaffold protein) it is derived from; said initial or scaffold protein may be the wild-type meganuclease or a mutant thereof." (The '372 patent at column 6, lines 45-50.)

16. In other words, the '372 patent states that, where the scaffold protein is wild-type I-CreI, modified DNA cleavage specificity can be determined by whether the wild-type I-CreI has the ability to cleave the same target site that the I-CreI meganuclease variant has the ability to cleave, under the same conditions. In addition, the '372 patent recognizes that an I-CreI meganuclease variant can itself be used as a scaffold protein for inducing further mutations and preparing a further I-CreI meganuclease variant to be used in the goal genetic engineering method or application. (The '372 patent at, *e.g.*, column 11, lines 3-10.) In such a case, modified DNA cleavage specificity can be determined by whether the first such variant has the

ability to cleave the same target site that the further variant has the ability to cleave or whether wild-type I-CreI has the ability to cleave that same target site ("said initial or scaffold protein may be the wild-type meganuclease or a mutant thereof"), again under the same conditions.

17. As explained in the '372 patent's specification and claims (*e.g.*, claims 4, 22 and 40), mutations (such as substitutions) of wild-type I-CreI result in a variant able to cleave a target site that is modified (relative to the target site of wild-type I-CreI) in at least one nucleotide in positions +/- 3 to 5. The +/- 3 to 5 positions of the wild-type I-CreI target site are numbered as shown in **Figure 2** (attached), which is a depiction of the wild-type I-CreI target site. As shown in **Figure 2**, in the wild-type target site, the nucleotides at positions -5 to -3 are GTC and the nucleotides at positions +3 to +5 are GAC. "A", "T," "C" and "G" are well-known abbreviations to a person of ordinary skill in the art for the building blocks of DNA – adenine, thymine, cytosine and guanine, respectively. An I-CreI meganuclease variant according to the '372 patent's specification and claims would have the ability to cleave a target site with at least one nucleotide changed in these +/- 3 to 5 positions, which target site is not capable of being cleaved, for example, by wild-type I-CreI, under the same conditions. *See* **Figures 2 & 3** (attached).

18. The specification and claims of the '372 patent are directed to I-CreI meganuclease variants that are homodimers, heterodimers and/or single-chains. As explained above, wild-type I-CreI comprises two monomers that are identical (having the same amino acid sequence) and are non-covalently associated with one another. According to the '372 patent's specification and claims, I-CreI meganuclease variants can be prepared in homodimer form, wherein each monomer is identical (having at least one mutation, including at least one substitution at one or more of amino acid positions 44, 68 and/or 70, and the monomer has at least one additional mutation at one or more of amino acid positions 26, 28, 30, 32, 33 and/or 38

(with the foregoing positions measured by counting the amino acids relative to the wild-type I-CreI sequence)). Such a homodimer I-CreI meganuclease variant can be pictured as A•A, with each A being the identical, mutated monomer and the "•" representing the non-covalent bonding or association of those two identical "A" monomers.

19. In addition, according to the '372 patent's specification and claims, I-CreI meganuclease variants can be prepared in heterodimer form, wherein each of the two monomers will have different amino acid sequences (relative to one another). At least one such monomer (or domain) in the heterodimer will have at least one mutation, including at least one substitution at one or more of amino acid positions 44, 68 and/or 70, and the monomer has at least one additional mutation at one or more of amino acid positions 26, 28, 30, 32, 33 and/or 38 (with the foregoing positions measured by counting the amino acids relative to the wild-type I-CreI sequence). Such a heterodimer I-CreI meganuclease variant can be pictured as A•B or B•A, with each of the A and B monomers having a different amino acid sequence from the other and the "•" representing the non-covalent bonding or association of those two different "A" and "B" monomers.

20. Moreover, as set forth in the '372 patent's specification and claims, it is also possible to prepare an I-CreI meganuclease variant known as a single-chain meganuclease. In such a configuration, the "A" and "B" monomers described above are covalently bonded to one another using a linker sequence, resulting in a single protein comprised of two monomers (for example, A and A, A and B, B and A, or B and B) associated with one another through that linker (*e.g.*, an amino acid sequence). Such a single-chain I-CreI meganuclease variant can be pictured, for example, as A∩A, A∩B, B∩A, and/or B∩B, with each of the A and B monomers having a different amino acid sequence from the other and the "∩" representing the association

or covalent bonding (through a linker) of the two monomers. In the example of an A∩B single-chain I-CreI meganuclease variant according to the '372 patent's specification and claims, at least one such monomer (or domain) in the single-chain will have at least one mutation, including at least one substitution at one or more of amino acid positions 44, 68 and/or 70, and the monomer has at least one additional mutation at one or more of amino acid positions 26, 28, 30, 32, 33 and/or 38 (with the foregoing positions measured by counting the amino acids relative to the wild-type I-CreI sequence). In the examples of A∩B and B∩B single-chain I-CreI meganuclease variants according to the '372 patent's specification and claims, both of the A and B monomers would have at least the foregoing mutations relative to wild-type I-CreI.

21. Thus, for example, claim 37 of the '372 patent (which is reproduced in full, just below this paragraph for convenience) specifies a "recombinant monomer of an I-CreI meganuclease variant" comprising at least one mutation, including at least one substitution at one or more of amino acid positions 44, 68 and/or 70, and the monomer has at least one additional mutation at one or more of amino acid positions 26, 28, 30, 32, 33 and/or 38 (with the foregoing positions measured by counting the amino acids relative to the wild-type I-CreI sequence), and further states that the "monomer when in dimeric form is able to cleave DNA." (The '372 patent at column 68, lines 37-48.) I understand that the parties have agreed that the phrase "when in dimeric form" means "when two monomers are associated," and I agree that one of ordinary skill in the art would have the same understanding. For example, such a person would understand that the monomer of claim 37 can be non-covalently associated with another monomer (as explained and depicted in **Figure 2**, for example, by the A•A homodimer and A•B heterodimer I-CreI meganuclease variants, which each are non-covalent associations between two monomers) or covalently associated through a linker with another monomer (as explained and depicted in

Figure 3, for example, by the A∩B and A∩A single-chain I-CreI meganuclease variants, which is a covalent association between two monomers through a linker).

> 37. A recombinant monomer of an I-CreI meganuclease variant comprising at least one mutation in the amino acid sequence of SEQ ID NO: 70, wherein said at least one mutation comprises a substitution at one or more of the amino acids residues at positions 44, 68 and 70 and said monomer further comprises at least one additional mutation of an amino acid residue directly contacting a DNA target sequence wherein said amino acid residue directly contacting a DNA target sequence is selected from the group consisting of positions 26, 28, 30, 32, 33 and 38, wherein said monomer when in a dimeric form is able to cleave DNA.

22. Finally, in **Figure 4** (attached) I present diagrams to demonstrate how, in accordance with the '372 patent, an I-CreI meganuclease variant is capable of recognizing and cleaving its intended DNA target site, while the same site is not capable of being cleaved by a scaffold I-CreI from which it is derived (demonstrating its "modified DNA cleavage specificity," according to the '372 patent).

ADDITIONAL CLAIM TERMS IN THE '372 PATENT

23. I reviewed the parties' Joint Chart in connection with the preparation of this declaration. Based on my review of the Joint Chart, as well as my independent review of the '372 patent, its prosecution histories and the other materials referenced in this declaration, along with my own experience and expertise, I agree with the claim meanings proposed by Cellectis in the Joint Chart and do not agree with the different meanings proposed by Precision. I also understand that, at the same time that I am submitting this declaration, Precision will submit a paper further explaining its positions on the meaning of these disputed claim terms, and I therefore reserve my right to address Precision's positions and further present my own in later declarations and/or in any expert reports or testimony that I may provide in this case.

24. As an initial matter, I note that it is my opinion that the language of the claims of the '372 patent is straightforward and would be clear to a person of ordinary skill in the art on

reading it and the patent's specification, based on the plain and well-understood ordinary meanings of the terms used in those claims. Therefore, in my view there is no need to interpret any of the claims in the '372 patent, since the meanings of those claims would be clear to such a person of ordinary skill in the art. I offer the opinions in this declaration to support that plain and ordinary meaning, including through reference to consistent passages in the specification of the '372 patent, and also because, in my opinion, Precision has offered different meanings in the Joint Chart that depart from the plain meanings of the claim terms and are inconsistent with the '372 patent's specification.

25. In the below paragraphs, I present the claim terms that I understand to be disputed by the parties in the Joint Chart (on the left-hand side) and the meaning of that disputed term to a person of ordinary skill in the art, which in my view also comports with the plain and ordinary meaning of each such term in the art to which the '372 patent pertains. While my below charts present the claim terms separately from the claim language as a whole in which those terms appear, in my analysis for this declaration I considered the meanings of each of these terms in the context of the entire claim (or claims) in which those terms appear, as well as in the context of the '372 patent's specification and prosecution history.

26. For all of the claim terms in the '372 patent that are not part of the Joint Chart, it is my opinion after reviewing all of the claims in the '372 patent that those terms are clear from their plain language to a person of ordinary skill in the art and, therefore, should be given their ordinary and customary meanings to such a person.

27. I understand claims 1, 19 and 37 of the '372 patent are referred to as "independent claims" because they do not reference any other claims in the patent, meaning that all of the elements in the claim are presented within the body of each of those claims 1, 19 and 37. I

understand that the remaining claims in the '372 patent are referred to as "dependent claims" because they refer to and "depend on" at least one other claim in the '372 patent to which they make reference. For example, claim 4 is dependent on claim 1 of the '372 patent, as demonstrated by claim 4's opening language of "[t]he monomer of an I-CreI meganuclease variant of claim 1 . . . ." I understand that this reference, for example, means that claim 4 contains all of the elements of claim 1, along with all of the additional elements specified in claim 4. I have reviewed and considered the claims of the '372 patent with the foregoing principles in mind. I have considered each of claims 1-54 of the '372 patent for this declaration and my opinions on the meanings of claim terms to a person of ordinary skill in the art applies to all 54 of those claims.

28. I understand that certain amendments to the claims of the '372 patent have been proposed during the reexamination of that patent in the PTO. For example, claims 4, 22 and 40 have been proposed to be cancelled, and all of their respective elements (directed to "modified DNA cleavage specificity . . .") have been proposed to be included by amendment into claims 1, 19 and 37, respectively. Those amendments would change the content of other claims in the '372 patent that depend from claims 1, 19 and 37. For example, claims that depend from claim 1 in the '372 patent would include the foregoing "modified DNA cleavage specificity . . ." language of claim 4 under such an amendment. My opinions on claim meanings are offered with regard to the claims as they issued in the '372 patent. If the claims of the '372 patent are amended as proposed, my opinions regarding the meanings of the claim terms identified in this declaration would remain the same. However, I reserve my right to provide a further declaration, report or testimony with respect to any such amended claims in the future.

29.

Claim Term	Meaning
monomer of an I-CreI meganuclease variant	a polypeptide from an I-CreI meganuclease variant

30. The claim term "monomer of an I-CreI meganuclease variant" is recited in claims 1-5, 19-23, and 37-41 of the '372 patent, and is also included in dependent claims 6-18, 24-36, and 42-54, each of which references one of the foregoing claims. A "monomer" is a well-known term in this field and would be understood by a person of ordinary skill in the art to which the '372 patent pertains as "a molecular building block – *e.g.*, a polypeptide – that can be associated with another to form a larger molecule," which in fact is the agreed upon definition for monomer in the Glossary of Agreed Upon Terms in the Joint Chart that I considered in preparing this declaration. "Monomer" by its plain language and singular tense refers to only one monomer or polypeptide, as opposed to two polypeptides as Precision suggests in the Joint Chart. In addition, I find no basis in the claim language, the '372 patent's specification or elsewhere for Precision's proposal in the Joint Chart that the above language is limited to a homodimer of two monomers or polypeptides that can act together. For example, as I explained above with regard to claim 37 (which contains the phrase "recombinant monomer of an I-CreI meganuclease variant"), the claimed recombinant monomer can be part of a homodimer, heterodimer or single-chain I-CreI meganuclease variant, according to the '372 patent.

31.

Claim Term	Meaning
monomer of an I-CreI meganuclease variant comprising at least one mutation in the amino acid sequence of SEQ ID NO: 70, wherein said at least one mutation comprises a substitution at one or more of the amino acids residues at positions 44, 68 and 70 and said monomer further comprises at least one additional mutation of an amino acid residue directly contacting a DNA target sequence wherein said amino acid residue directly contacting a DNA target sequence is selected from the group consisting of positions 26, 28, 30, 32, 33 and 38	monomer of an I-CreI meganuclease variant comprising at least one mutation in the amino acid sequence of SEQ ID NO: 70, wherein said at least one mutation comprises a substitution at one or more of the amino acid residues at positions 44, 68 and 70 with reference to the amino acid numbering of SwissProt accession number P05725 or pdb accession code 1g9y and said monomer further comprises at least one additional mutation of an amino acid residue at positions 26, 28, 30, 32, 33 or 38 with reference to the amino acid numbering of SwissProt accession number P05725 or pdb accession code 1g9y

32. Claims 1, 19 and 37 are independent claims in the '372 patent and each of them recites the above claim term, which includes identification of amino acid residues for mutations at various numbered positions. This claim term is also included in dependent claims 2-18, 20-36, and 38-54, each of which references one of the foregoing claims. The patent's specification is clear that the numbering of such amino acid residues in the claim is done with reference to the amino acid numbering of SwissProt accession number P05725 or pdb accession code 1g9y, which are the wild-type I-CreI. (The '372 patent at column 5, lines 43-46.) A person of ordinary skill in the art would recognize and understand this numbering convention from reading the '372 patent and would apply that numbering convention to the amino acid positions to be mutated or substituted on SEQ ID NO. 70, which has an extra Alanine ("Ala" or "A") at position 2. Because it is not present in wild-type I-CreI, and given the express numbering guidance in the '372 patent specification, that extra Alanine would be disregarded by a person of ordinary skill in the art in counting the amino acid sequence of SEQ ID NO. 70 relative the amino acid positions

specified in the above claim term. Finally, from the plain language of the above claim term (*e.g.*, "comprising at least one mutation in the amino acid sequence of SEQ ID NO: 70"), one of ordinary skill in the art would understand that additional mutations can be made to the monomer of SEQ ID NO. 70 beyond the substitutions and mutations at positions specifically set forth by number in the above claim term.

33.

Claim Term	Meaning
modified DNA cleavage specificity relative to the I-CreI meganuclease of SEQ ID NO: 70 in at least one nucleotide in the +/- 3 to 5 triplets	having the ability to cleave a DNA target site that has at least one nucleotide mutation in the gtc triplet at positions -5 to -3 or the gac triplet at positions +3 to +5, where the DNA target site is not cleaved in the same conditions by an initial meganuclease scaffold

34. The above claim term is recited in claims 4, 22 and 40. "Modified specificity" is explicitly defined in the specification as a "meganuclease variant able to cleave a homing site that is not cleaved in the same conditions by the initial meganuclease (scaffold protein) it is derived from; said initial or scaffold protein may be the wild-type meganuclease or a mutant thereof." (The '372 patent at, *e.g.*, column 6, lines 45-50.) As I discussed above, claims of the '372 patent (*e.g.*, claims 4, 22 and 40) also specify that the monomer of an I-CreI meganuclease variant, when in dimeric form, has the ability to cleave a modified target site. One of ordinary skill in the art would understand that where the scaffold protein is wild-type I-CreI, modified DNA cleavage specificity for an I-CreI meganuclease variant is determined by whether the wild-type I-CreI has the ability to cleave the same target site as the I-CreI meganuclease variant is capable of cleaving, under the same conditions. An I-CreI meganuclease variant having the recited "modified DNA cleavage specificity" in the claims would have the ability to cleave a

target site with at least one nucleotide changed in these +/- 3 to 5 positions, which target site is not capable of being cleaved, for example, by wild-type I-CreI under the same conditions. A person of such skill would also understand from reading the '372 patent that an I-CreI meganuclease variant can itself be used as a scaffold protein for inducing further mutations and preparing a further I-CreI meganuclease variant. In such a case, modified DNA cleavage specificity can be determined by whether the first such variant has the ability to cleave the same target site (with at least one nucleotide changed in the specified +/- 3 to 5 positions) that the further variant has the ability to cleave or whether wild-type I-CreI has the ability to cleave that same target site ("said initial or scaffold protein may be the wild-type meganuclease or a mutant thereof"), again under the same conditions. For all of these reasons, one of ordinary skill in the art would understand the above claim term to have the indicated meaning in the chart, including that "an initial meganuclease scaffold" includes wild-type I-CreI or another I-CreI meganuclease variant used as a scaffold, based on the plain language of that term and the express guidance of the specification.

35.

Claim Term	Meaning
A44/A68/A70 . . . T44/S68/K70 (abbreviated for convenience – please see full '372 patent for entire term)	The nomenclature "X"44/"Y"68/"Z"70 means a variant monomer having amino acid residues, "X," "Y" and "Z" at position 44, 68 and 70 with reference to the amino acid numbering of SwissProt accession number P05725 or pdb accession code 1g9y

36. The term "A44/A68/A70 . . . T44/S68/K70" is recited in claims 5, 23 and 41 of the '372 Patent. As discussed above, the specification of the '372 patent is very clear with regard to numbering of amino acid positions in the claimed monomers of an I-CreI meganuclease

variant. A person of ordinary skill in the art reading the specification would immediately understand that the above meaning of the claim term, namely that all such numbering of amino acid positions, is done with reference to the amino acid numbering of SwissProt accession number P05725 or pdb accession code 1g9y, the wild-type I-CreI. (The '372 patent at column 5, lines 43-46.)

37.

Claim Term	Meaning
single-chain chimeric meganuclease comprising [a] fusion of [two monomers]	a meganuclease in the form of a single protein comprising a first monomer fused to a second monomer

38. The claim term "single-chain chimeric meganuclease comprising [a] fusion of [two monomers]" is recited in claims 13-18, 31-36, and 49-54 of the '372 patent. A person of ordinary skill in the art would understand this term from its plain language to mean "a meganuclease in the form of a single protein comprising a first monomer fused to a second monomer." Moreover, the specification of the '372 patent teaches that I-CreI meganucleases are proteins. (*See, e.g.*, the '372 patent at column 3, lines 17-22; column 11, lines 11-17; column 17, lines 11; column 17, lines 27-35; column 17, line 66 to column 18, line 20; column 22, lines 17-30; column 24, lines 18-23; column 27, lines 20-33; column 28, lines 23-25; and column 28, lines 34-38.) In my opinion it is clear from the specification that single-chain chimeric meganuclease should be understood to be a protein, which has a function, versus a polypeptide which may not necessarily have a function. Thus, this term would mean a protein to a person of ordinary skill in the art, not a polypeptide as Precision suggests in the Joint Chart. In fact, as I explain above, a person of ordinary skill in the art would understand that a single-chain meganuclease, as specified in the above chart, is comprised of two domains, each corresponding

to a monomer, that are covalently associated through a linker sequence (depicted A∩A or A∩B, for example, at **Figure 3**), which is the same as the "fusion" of the two such monomers (or polypeptides) specified in the above claim term.

39.

Claim Term	Meaning
wild-type monomer from I-DmoI	a naturally occurring amino acid sequence from I-DmoI that has the ability to cleave DNA when in dimeric form with a monomer of I-CreI

40. The term "wild-type monomer from I-DmoI" is recited in claims 7, 11-13, 17-18, 25, 29-31, 35-36, 43, 47-49, and 53-54. I-DmoI exists as a single-chain endonuclease in the wild, as a person of ordinary skill in the art would understand and appreciate. Such a person would also understand that wild-type I-DmoI has two domains that are each structurally equivalent to an I-CreI monomer. Therefore, from the plain language of the above claim term, such a person would understand that the reference to a "wild-type monomer from I-DmoI" means a naturally occurring amino acid sequence from I-DmoI, but is not limited to the entire sequence of the I-DmoI protein as found in the wild. A person of ordinary skill in the art would understand that any naturally occurring amino acid sequence corresponding to either domain of I-DmoI that has the ability to cleave DNA when in dimeric form with a monomer of I-CreI is included in the above term. One reason that I disagree with Precision's proposal for the meaning of this term in the Joint Chart is that Precision limits the term to the amino acid sequence of PDB accession number 1b24, which does not appear anywhere in the '372 patent and constitutes the amino acid sequence for the entire wild-type I-DmoI. For all of the reasons discussed above regarding the meaning of the term "monomer" to a person of ordinary skill in the art, Precision's

definition does not make sense because it would turn a single "monomer" into an entire single-chain protein (comprised of two monomers) and limit it to the same definition.

41.

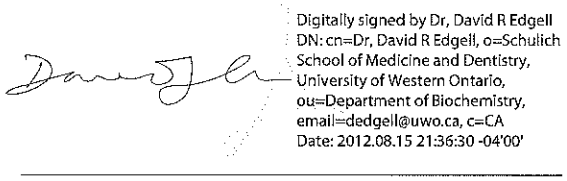
Claim Term	Meaning
variant of the wild-type monomer from I-CreI	a mutant monomer of I-CreI, which when in dimeric form, retains the ability to cleave DNA

Claim Term	Meaning
variant of the wild-type monomer from I-DmoI	a mutant monomer of I-DmoI that has the ability to cleave DNA when in dimeric form with a monomer of I-CreI

42. The term "variant of the wild-type monomer from I-CreI" appears in claims 7, 10, 13, 16, 25, 28, 31, 34, 43, 46, 49, and 52. The term "variant of the wild-type monomer from I-DmoI" appears in claims 7, 12-13, 18, 25, 30-31, 36, 43, 48-49, and 54. I have grouped these two claim terms because I understand from the Joint Chart that Precision contends that these two terms are indefinite. I disagree with Precision. In my opinion, the meanings of both of the above terms would be clear to a person of ordinary skill in the art from their plain language. The terms "variant of the wild-type monomer from I-CreI" and "variant of the wild-type monomer from I-DmoI" are also clear from the language of the patent specification (the '372 patent at column 1, lines 13-19, and column 7, lines 45-50) and through the background knowledge possessed by those of ordinary skill in the art when the application was filed. Such a person of ordinary skill in the art would have understood that a "variant of the wild-type monomer from I-CreI" was a mutant monomer of I-CreI, which when associated with a second monomer, retains the ability to

cleave DNA (since each of the above claims containing this language specifies a meganuclease variant that is a heterodimer or a single-chain, which such a person would understand in each instance requires association of two monomers). Similarly, one of ordinary skill in the art would have understood that a "variant of the wild-type monomer from I-DmoI" was a mutant monomer of I-DmoI that has the ability to cleave DNA when in association with a monomer of I-CreI (since each of the above claims containing this language specifies a meganuclease variant that is a heterodimer or a single-chain, which such a person would understand in each instance requires association of two monomers). Indeed, both of these terms are clear from their plain language and from the '372 patent as a whole, which is directed to such variant or mutant monomers as part of creating meganuclease variants for use in genetic engineering.

I declare under penalty of perjury that the foregoing is true and correct to the best of my knowledge.



Executed on August 15, 2012

David Edgell, Ph.D.

CERTIFICATE OF SERVICE

I hereby certify that on August 15, 2012, I electronically filed the foregoing document with the Clerk of the Court using CM/ECF and have also served the parties below as noted:

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